L4 ANSWER 12 OF 12 DGENE COPYRIGHT 2004 The Thomson Corp on STN
ACCESSION NUMBER: AAY95896 Peptide DGENE
TITLE: Regulating mucus secretion by a mucus-secreting cell, useful for treating e.g. bronchitis, asthma or pneumonia, by administering a compound that inhibits or enhances myristolated alanine-rich C-kinase substrate protein -
INVENTOR: Li Y; Martin L D; Adler K B
PATENT ASSIGNEE: (UYNC-N)UNIV NORTH CAROLINA STATE.
PATENT INFO: WO 2000050062 A2 20000831 66p
APPLICATION INFO: WO 2000-US5050 20000224
PRIORITY INFO: US 1999-256154 19990224
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-572036 [53]
DESCRIPTION: MANS peptide inhibitor of MARCKS-related mucus secretion.
AB The present sequence is that of **MANS** peptide, comprising the N-terminal region of human myristoylated alanine-rich C kinase substrate MARCKS protein (see AAY95898), a major cellular substrate for protein kinase S. **MANS** peptide inhibits **secretion** of mucus from mucus membranes and mucus-**secreting** cells, including human **airway** epithelial cells. It is suggested to block attachment of MARCKS protein to the mucin granule, thus blocking or inhibitng the release of mucin granules and the **secretion** of mucus by the cell. The invention relates to methods and compounds for decreasing mucus **secretion**, particularly in the **airways**. Such compounds include **MANS** peptide and antisense oligonucleotides to MARCKS. They are useful in inhibiting mucus **secretion** in conditions such as bronchitis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, emphysema, pneumonia, influenza, rhinitis and the common cold.
AB The present sequence is that of **MANS** peptide, comprising the N-terminal region of human myristoylated alanine-rich C kinase substrate MARCKS protein (see AAY95898), a major cellular substrate for protein kinase S. **MANS** peptide inhibits **secretion** of mucus from mucus membranes and mucus-**secreting** cells, including human **airway** epithelial cells. It is suggested to block attachment of MARCKS protein to the mucin granule, thus blocking or inhibitng the release of mucin granules and the **secretion** of mucus by the cell. The invention relates to methods and compounds for decreasing mucus **secretion**, particularly in the **airways**. Such compounds include **MANS** peptide and antisense oligonucleotides to MARCKS. They are useful in inhibiting mucus **secretion** in conditions such as bronchitis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, emphysema, pneumonia, influenza, rhinitis and the common

L8 ANSWER 8 OF 14 DISSABS COPYRIGHT (C) 2004 ProQuest Information and Learning Company; All Rights Reserved on STN

ACCESSION NUMBER: 2000:39962 DISSABS Order Number: AAI9960139

TITLE: **MARCKS** protein, a key intracellular molecule controlling mucin **secretion** by human **airway** epithelial cells

AUTHOR: Li, Yuehua [Ph.D.]; Adler, Kenneth B. [adviser]

CORPORATE SOURCE: North Carolina State University (0155)

SOURCE: Dissertation Abstracts International, (1999) Vol. 61, No. 2B, p. 639. Order No.: AAI9960139. 100 pages.

DOCUMENT TYPE: Dissertation

FILE SEGMENT: DAI

LANGUAGE: English

AB Excess **secretion** of mucin (the major glycoprotein component of mucus) by **airway** epithelium and submucosal glands is associated with a number of respiratory diseases and **airway** obstruction. Despite identification of various mucin **secretagogues**, a common signaling pathway and intracellular molecule(s) linking **secretagogue** action to mucin granule release have not been elucidated. Here it is shown that the myristoylated alanine-rich C kinase substrate (**MARCKS**) is a pivotal, convergent signaling molecule mediating mucin **secretion** in human **airway** epithelial cells. **MARCKS** is known as a widely distributed cellular substrate for protein kinase C (PKC). It can also crosslink actin filaments, and therefore has been implicated in a variety of biological processes requiring actin cytoskeleton involvement. However, definitive function(s) of **MARCKS** in intact cells is not clear. This dissertation presents the first direct evidence to reveal a specific functional role for **MARCKS** in a physiological process.

Data presented in this dissertation demonstrate that mucin **secretion** by normal human bronchial epithelial (NHBE) cells involves activation of two separate protein kinases: PKC and cGMP-dependent protein kinase (PKG), and **MARCKS** serves as a "cross-bridge" integrating the effects of these two protein kinases, thereby controlling mucin granule movement and exocytosis. The specific signaling mechanism suggested by the experimental results is that activation of PKC leads to phosphorylation of **MARCKS**, resulting in translocation of **MARCKS** from the plasma membrane to the cytoplasm, where **MARCKS** is targeted to the mucin granule membrane with the assistance of **MARCKS**-associated proteins. Activated PKG in turn activates a cytoplasmic protein phosphatase 2A, which dephosphorylates **MARCKS**, stabilizing its attachment to the granule membrane and allowing **MARCKS** to crosslink actin filaments, thereby tethering the granule to the cytoskeleton for exocytosis. These research findings may greatly aid in development of novel drugs and new therapies for **airway** diseases characterized by mucus hypersecretion.

TI **MARCKS** protein, a key intracellular molecule controlling mucin **secretion** by human **airway** epithelial cells

AB Excess **secretion** of mucin (the major glycoprotein component of mucus) by **airway** epithelium and submucosal glands is associated with a number of respiratory diseases and **airway** obstruction. Despite identification of various mucin **secretagogues**, a common signaling pathway and intracellular molecule(s) linking **secretagogue** action to mucin granule release have not been elucidated. Here it is shown that the myristoylated alanine-rich C kinase substrate (**MARCKS**) is a pivotal, convergent signaling molecule mediating mucin **secretion** in human **airway** epithelial cells. **MARCKS** is known as a widely distributed cellular substrate for protein kinase C (PKC). It can also crosslink actin filaments, and therefore has been implicated in a variety of biological processes requiring actin cytoskeleton involvement. However, definitive function(s) of **MARCKS** in intact cells is not clear. This

dissertation presents the first direct evidence to reveal a specific functional role for **MARCKS** in a physiological process.

Data presented in this dissertation demonstrate that mucin **secretion** by normal human bronchial epithelial (NHBE) cells involves activation of two separate protein kinases: PKC and cGMP-dependent protein kinase (PKG), and **MARCKS** serves as a "cross-bridge" integrating the effects of these two protein kinases, thereby controlling mucin granule movement and exocytosis. The specific signaling mechanism suggested by the experimental results is that activation of PKC leads to phosphorylation of **MARCKS**, resulting in translocation of **MARCKS** from the plasma membrane to the cytoplasm, where **MARCKS** is targeted to the mucin granule membrane with the assistance of **MARCKS**-associated proteins. Activated PKG in turn activates a cytoplasmic protein phosphatase 2A, which dephosphorylates **MARCKS**, stabilizing its attachment to the granule membrane and allowing **MARCKS** to crosslink actin filaments, thereby tethering the granule to the cytoskeleton for exocytosis. These research findings may greatly aid in development of novel drugs and new therapies for **airway** diseases characterized by mucus hypersecretion.

ANSWER 6 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:697269 CAPLUS
DOCUMENT NUMBER: 136:115748
TITLE: **MARCKS** protein: A potential modulator of **airway** mucin **secretion**
AUTHOR(S): Li, Yuehua; Martin, Linda D.; Adler, Kenneth B.
CORPORATE SOURCE: College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA
SOURCE: Cilia and Mucus: From Development to Respiratory Defense, [International Meeting], 2nd, Sirmione, Italy, Nov. 3-4, 1999 (2001), Meeting Date 1999, 179-193. Editor(s): Salathe, Matthias. Marcel Dekker, Inc.: New York, N. Y.
CODEN: 69BVC5
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review on myristoylated alanine-rich C kinase substrate protein, and on a rationale for looking at **MARCKS** protein as a potentially important regulator of **airway** mucin **secretion**. MARCKS protein was identified as a specific in vitro and in vivo substrate for protein kinase C. The preliminary study of a potential role for **MARCKS** protein in the process of **airway** mucin **secretion** showed that it is involved in the **secretory** pathway and could be a major convergent mol. in intracellular signaling leading to mucin granule transport and exocytosis in human globlet cells in vitro.

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **MARCKS** protein: A potential modulator of **airway** mucin **secretion**

AB A review on myristoylated alanine-rich C kinase substrate protein, and on a rationale for looking at **MARCKS** protein as a potentially important regulator of **airway** mucin **secretion**. MARCKS protein was identified as a specific in vitro and in vivo substrate for protein kinase C. The preliminary study of a potential role for **MARCKS** protein in the process of **airway** mucin **secretion** showed that it is involved in the **secretory** pathway and could be a major convergent mol. in intracellular signaling leading to mucin granule transport and exocytosis in human globlet cells in vitro.

IT Respiratory tract
(**MARCKS** protein: A potential modulator of **airway** mucin **secretion**)

IT **MARCKS** (myristoylated alanine-rich C kinase substrate)
Mucins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**MARCKS** protein: A potential modulator of **airway** mucin **secretion**)